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Managing trichomonal vaginitis refractory to conventional treatment with metronidazole

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SUMMARY Three patients with vulvovaginitis caused by *Trichomonas vaginalis*, which was refractory to conventional treatment with metronidazole are described. The *T vaginalis* strain isolated from one patient was resistant to metronidazole (minimum inhibitory concentration (MIC) more than 100 mg/l) under aerobic conditions, although under anaerobic conditions it was as susceptible as a normal reference strain.

The effect of the concomitant use of other medication and the influence of other vaginal pathogens on the efficacy of metronidazole are highlighted.

Since its introduction in the 1960s, metronidazole has been the drug of choice for treating trichomonal infections. Alternative treatments are either ineffective or use drugs similar to metronidazole in structure and laboratory properties. Treatment regimens using metronidazole 200 mg three times a day by mouth for seven days[1] or, more recently, a 2 g single oral dose[2,3] have shown cure rates of about 90%, and resistance to metronidazole is uncommon.[4] The suggested treatment for those who fail to respond to the above routine treatment regimens is metronidazole 400 mg three times a day orally for seven days.

We report on three patients in whom treatment of symptomatic trichomonal vaginitis with metronidazole in regimens using up to twice the conventional doses failed to eradicate the infection. The reasons for the poor responses are highlighted, and a protocol for the management of such patients is proposed.

Patients and methods

We studied patients with persistent symptomatic trichomonal vaginitis that had failed to respond to conventional treatment with metronidazole, provided that reinfection or poor compliance were not considered to be the cause of treatment failure. Trichomoniasis was diagnosed by finding the organism in a saline mounted preparation of vaginal secretions or on culture using Feinberg and Whittington's medium. We tested the susceptibility to metronidazole of the organism and a reference strain using methods described by Meingassner and Thurner.[5] We measured serum metronidazole concentrations using a high pressure liquid chromatography (HPLC) assay as described by Kaye *et al.*[6]

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Case reports

Three women with vulvovaginitis due to *T vaginalis* were enrolled in the study. Their presenting symptoms were pruritus vulvae and vaginal discharge. On examination they had vulvovaginitis and a white discharge or frothy mucopus. Screening tests for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and serological tests for syphilis gave negative results, and group B haemolytic streptococci were isolated from high vaginal swabs from all three. They had all received numerous successive courses of treatment with metronidazole using conventional and double dose regimens, all of which had failed to eradicate the infection (table 1).

All three women denied having had further sexual activity since they first presented, and their compliance was considered to be satisfactory. Their sexual consorts, who were all symptomless, were treated epidemiologically with metronidazole 200 mg by mouth three times a day for seven days.

The strains of *T vaginalis* from all three patients showed mean inhibitory concentrations (MICs) of metronidazole similar to those of reference strains under anaerobic conditions. The strain from case 1,

Table 1 *No of courses of treatment received before entering the study*

Drug regimens	*Case 1*	*Case 2*	*Case 3*
Metronidazole:			
2 g single dose orally	1	3	1
200 mg orally three times a day × 7 days	2		2
400 mg orally three times a day × 7 days	1	2	1
800 mg twice daily plus 1 g vaginal pessary × 7 days		1	
500 mg rectal suppositories twice a day × 7 days	2		
500 mg intravenously three times a day × 7 days	1		
Tinidazole:			
500 mg twice a day × 7 days	1		

however, showed in vitro resistance under aerobic conditions (table 2). Serum zinc concentrations (normal range 12·7 to 20·2 μmol/l) were normal in cases 1 (16 μmol/l) and 3 (19·4 μmol/l) and low (10·6 μmol/l) in one patient (case 2), who was also having anticonvulsant treatment.

CASE 1

A single woman aged 21, who used no contraception, was admitted to hospital for further investigation and treatment under supervision because her symptoms were persistent. Treatment was commenced using metronidazole 1 g twice daily by mouth and a 500 mg metronidazole vaginal pessary once daily for 10 days. Her serum metronidazole concentrations were: 19·6 mg/l (trough level) and 25·6 mg/l (two hours after treatment) on day 2, and 26 mg/l (trough level) and 35·1 mg/l (two hours after treatment) on day 5. The regimen failed to eradicate the infection, and the patient remained symptomatic. Four months later she developed signs and symptoms suggestive of pelvic infection, and microbiological investigation confirmed the presence of *T vaginalis and* β haemolytic group B streptococci in her vaginal secretions. No other genital pathogens were isolated. Treatment for seven days with Augmentin 250 mg three times a day and metronidazole 1 g twice daily, both by mouth, and a 500 mg metronidazole vaginal pessary once a day brought about a resolution of her abdominal symptoms and eradicated the group B streptococci, but not the *T vaginalis*. *T vaginalis* was isolated from vaginal secretions on four occasions during the following eight weeks. Subsequent to this, however, the patient achieved spontaneous cure, became free of symptoms and the organism could no longer be isolated despite six attempts in eight weeks.

CASE 2

As this woman, who was 27, married, and using no contraceptive, had been taking long term carbamazepine and phenytoin for temporal lobe epilepsy, the possibility of interaction with oral anticonvulsants was considered. While she was taking a course of metronidazole 400 mg by mouth, serum concentrations were measured and found to be 14·8 mg/l half an hour, 13·8 mg/l one hour, and 11·2 mg/l two hours after treatment. As her symptoms and *T vaginalis* infection persisted, she was admitted to hospital for further investigation and treatment under supervision. Group B streptococci were not isolated on this occasion. Treatment with metronidazole 500 mg intravenously three times a day was started, and serum concentrations were: 5·9 mg/l (trough level) and 18·9 mg/l one hour and 9·4 mg/l four and a half hours after treatment. Within 48 hours she became free of symptoms and *T vaginalis* was no longer isolated from her vaginal secretions. After four days of intravenous treatment she was given metronidazole 500 mg rectal suppositories twice daily for a further four days. Serum metronidazole concentrations while she was using suppositories were: 5·6 mg/l (trough level) and 7·1 mg/l one hour and 22 mg/l three hours after treatment. She remained free of symptoms, and weekly attempts to isolate the organism were unsuccessful during a four week follow up period.

CASE 3

To assess the compliance of this woman, who was 29, married, and using oral contraception, and to exclude inadequate absorption of the drug, serum metronidazole concentrations were measured after an oral dose of 400 mg and found to be 8·8 mg/l one hour later. As her symptoms persisted, a further course of treatment with 2 g metronidazole (single dose) combined with oxytetracycline 250 mg four times a day was administered for seven days. This eradicated the group B streptococci but not the *T vaginalis*. A further seven day course of metronidazole 400 mg orally three times a day and one povidone iodine vaginal pessary a day eradicated the infection, and the patient became free of symptoms. Samples of vaginal secretions taken weekly for the following four weeks failed to show *T vaginalis*.

Discussion

Though several workers have reported cases of *T vaginalis* refractory to treatment with metronidazole,

Table 2 *Minimum inhibitory concentrations (mg/l) of metronidazole for strains of Trichomonas vaginalis*

Conditions	*Reference strain*	*Strains from:* *Case 1*	*Case 2*	*Case 3*
Anaerobic	< 2	< 2	< 2	< 2
Aerobic	< 2	> 100	< 2	< 3

true resistance of the organism to the drug is generally regarded as being uncommon.[5 7-10 14] Failure to eradicate the organism has been attributed to: poor patient compliance; reinfection by an untreated consort or a new consort; defective absorption of metronidazole (in the absence of a definite malabsorption syndrome, this appears to be a rare cause of treatment failure as most oral preparations of metronidazole have shown good absorption[11] and bioavailability[12]); interference by other organisms present in the vaginal secretions;[13] possible drug interaction; low serum zinc concentrations;[7] and true resistance to metronidazole.[5 7-10 14]

We examined our patients in view of the above points. In all three patients, poor compliance and reinfection were not considered to be applicable. As all three had high serum concentrations of metronidazole after oral (and in case 2 after rectal) administration of the drug, defective absorption was excluded. Serum zinc concentrations were measured and found to be normal in two patients and low in one (case 2), who was also taking anticonvulsant treatment. Though

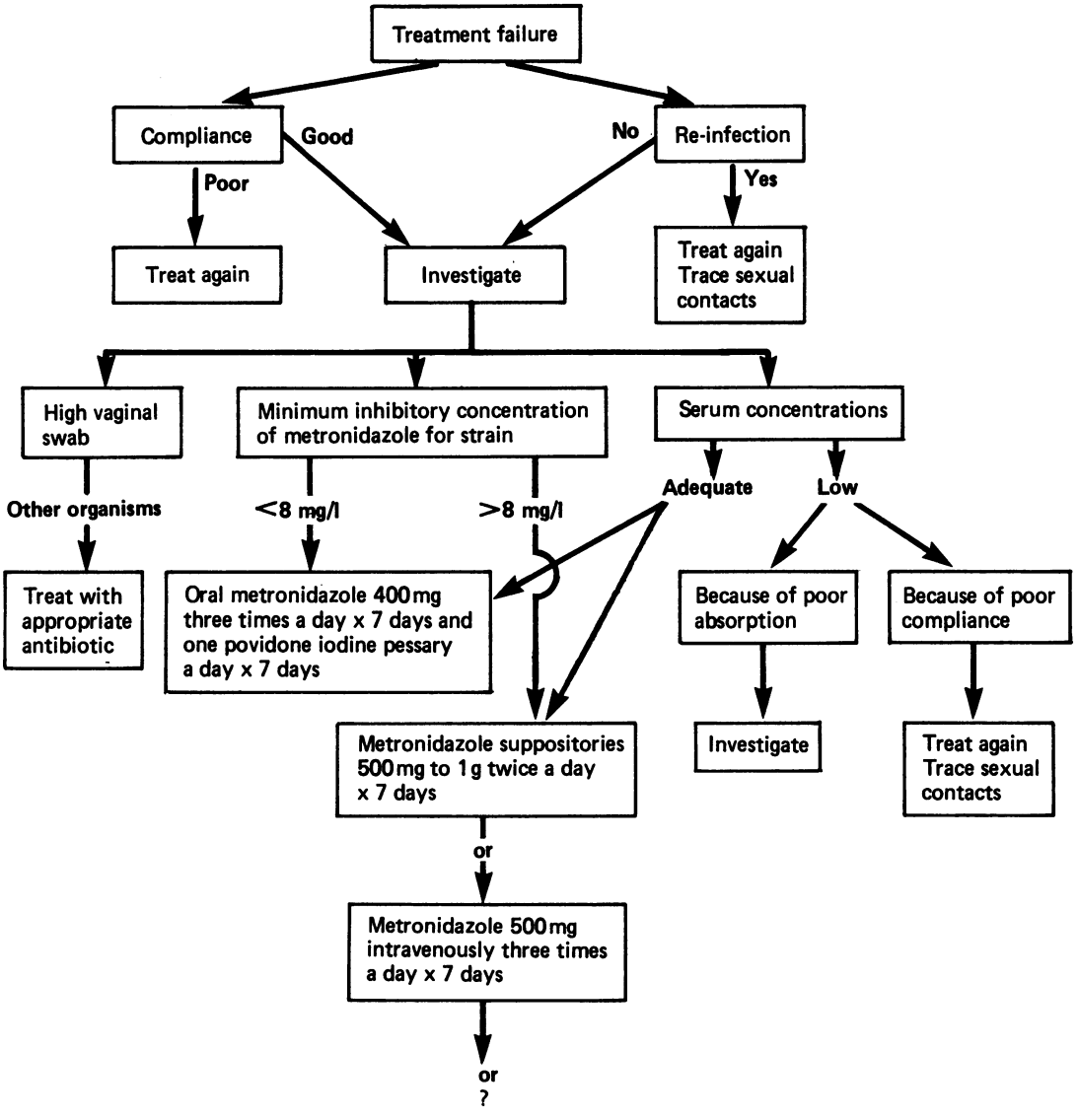

Figure *Protocol for managing women with trichomonal vaginitis refractory to conventional treatment with metronidazole.*

Barbeau and Donaldson reported low serum zinc concentrations in treated patients with epilepsy,[15] these findings have not been confirmed by other workers.[16] Though the serum zinc concentrations in case 2 were similar to those reported by Wilmott *et al*,[7] the patient was successfully treated without zinc supplementation.

Interference by other organisms present in vaginal secretions may have played an appreciable part in at least two of the treatment failures (cases 2 and 3). All three patients had group B streptococci in the vaginal secretions. Two (cases 1 and 3) had received broad range antibiotics before *T vaginalis* was successfully eradicated. Furthermore, in case 2, group B streptococci were not isolated from the culture of vaginal secretions performed just before the start of high dose metronidazole treatment that successfully eradicated *T vaginalis*. We cannot implicate specifically group B streptococci in this context, as one or more of the other vaginal commensals sensitive to broad range antibiotics may have played a part. Furthermore, Edwards *et al* have shown that several organisms, including aerobic organisms commonly found in the vagina, are capable of absorbing and inactivating appreciable amounts of metronidazole.[13]

MICs of metronidazole for the strains of *T vaginalis* from all three patients were similar to those for normal reference strains under anaerobic conditions, and only the strains from case 1 showed in vitro resistance under aerobic conditions. This observation is in keeping with that reported by several other workers.[5 17] We think, therefore, that the *T vaginalis* strain from case 1 was the only one that showed true resistance to metronidazole. The spontaneous resolution of the infection in that patient is difficult to explain because, as far as we know, she received no medication between being discharged from hospital after treatment for pelvic infection and becoming free of symptoms and having complete resolution of the infection. The patient attributed the success to her having taken up meditation after being discharged from hospital.

PROPOSED PROTOCOL FOR MANAGING TREATMENT FAILURES

Patients who have failed to respond to conventional treatment with metronidazole should be reassessed and managed as shown in the figure. Those who are poor compliers or have become reinfected by an untreated or a new consort should be treated again and their sexual consorts traced and treated. When poor compliance or reinfection are not thought to apply, patients should undergo further investigations. Vaginal secretions obtained with a high vaginal swab should be cultured for other organisms and, if results are positive, patients should be treated using appropriate antibiotics. The MIC of metronidazole for the *T vaginalis* strain and serum concentrations of metronidazole should be measured to ensure that absorption and patient compliance are adequate. Patients harbouring strains with MICs of metronidazole of less than 8 mg/l can be treated with metronidazole 400 mg orally three times a day and one povidone iodine vaginal pessary daily for seven days.

When strains have MICs of more than 8 mg/l metronidazole (that is, true resistance), a high dose metronidazole regimen using a 500 mg to 1 g rectal suppository twice a day for seven days or 500 mg intravenously three times a day for seven days should be prescribed. When the MIC is very high (for example, more than 100 mg/l as in case 1), the regimens stated above may not achieve the serum concentrations necessary to eradicate the infection. True resistance to metronidazole is fortunately still rare, and managing patients infected with such strains can be very difficult because no effective alternative treatment is yet available. This clearly shows the need for further research to find effective alternative treatment, as true resistance to metronidazole may well become more common.

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